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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
NGUYEN, BAO THUY L

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 10/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/005,710	VOJDANI, ARISTO	
	Examiner	Art Unit	
	Bao-Thuy L. Nguyen	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 8/30/2004 has been received. Claims 1-6 are pending.

2. The text of those US codes not found in this office action may be found in a previous office action.

Rejections Withdrawn

3. The rejection of claims 1-6 under the judicially created doctrine of obviousness-type double patenting is withdrawn in view of the corrected Terminal Disclaimer submitted 9/20/2004.

4. The rejection of claims 1-4 under 35 USC 102(b) as being anticipated by Kovanen et al is withdrawn in view of the amendment to claim 1. Kovanen fails to teach the detection of oxidized LDL in a saliva sample.

Rejections Maintained

Claim Rejections - 35 USC § 112, first paragraph

5. Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for detecting antibodies against certain auto antigens and for indicating the presence or possibility of cardiovascular disease, does not reasonably provide enablement for a method for prediction of early pathogenic reaction for a cardiovascular disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification teaches the detection of salivary IgA against several auto antigens that are alleged to be related to cardiovascular diseases. Any elevation in the level of IgA in patients' samples as compared to normal control subjects indicates possible cardiovascular disease. Nowhere in the specification is there a teaching of a method for prediction of early pathogenic reaction for a cardiovascular disease.

According to Strongin (1993, "Sensitivity, Specificity, and Predictive Value of Diagnostic Tests: Definitions and Clinical Applications", in Laboratory Diagnosis of Viral Infections, Lennette, e., ed., Marcel Dekker, Inc., New York, pp. 211-219) a number of characteristics need to be considered in the development of any suitable diagnostic assay. These characteristics include the following: (1) the sensitivity of the assay; (2) the true-positive test rate; (3) the false-negative test rate; (4) the specificity, or percentage of patients without the disease who will display a negative results; (5) the true-negative test rate; (6) the false-positive test rate; (7) the predictive value, or the probability that the test result is correctly indicating the presence or absence of the disease; (8) the prevalence, or number of patients in any given population that have the disease in question; (9) the efficiency or percentage of all results that are true; (10) the accuracy of the recited diagnostic assay. Additional considerations must also be examined to enable the clinician to practice the invention including assessment of the following: (1) when is the maximum sensitivity desired? (2) when is the maximum specificity desired?; (3) when is the maximum efficiency desired?; (4) How is the maximum sensitivity or specificity achieved?; (5) how is the predictive value maximized? An essential understanding of these factors is required to enable the skilled artisan to accurately use and interpret any given diagnostic test.

Since the specification lacks any teaching of a method for prediction of early pathogenic reaction for a cardiovascular disease, or any information regarding the patients from which the samples were taken, and whether any considerations were given to any of the characteristics state above, it would require undue experimentation for one skilled in the art to make and use the invention as claimed.

Because of the lack of description in the specification for the claimed method, the data presented in tables 2 and 3 and the examples cannot be used for the prediction of early pathogenic reaction for a cardiovascular disease.

Therefore, it is maintained that one of ordinary skill in the art could not make and use the invention as claimed without undue experimentation.

6. Claims 1 and 3-6 are further rejected because the specification is not enabling for a method of detecting antibodies against any and all auto antigens. Specifically, the specification discloses the detection of IgA against oxidized LDL, comparing the detected level to those of normal control subjects and any elevation in the level of IgA is diagnostic for a possibility of cardiovascular disease. The specification at pages 3-8 teaches that the development of autoimmunity to myocardial antigens, for example, has been recognized after myocardial infarction or after cardiac surgery. Furthermore, the specification discloses that oxidized LDL autoantibodies have been detected in the bloodstream of patients with coronary artery disease, etc. Nowhere in the specification is there a disclosure of any other autoantibodies against any other autoantigen, other than myosin, oxidized LDL, heat shock protein-60, β-2-glycoprotein-1, platelet glycoprotein, and certain immune complexes, as being diagnostic for cardiovascular disease.

Applicant asserts that amended claim 1 is fully supported by the specification, specifically the examples on pages 13-22; however, claim 1, even as amended, still broadly encompasses the detection of any and all autoantibodies against any and all autoantigens in a saliva sample. Claim 1 is not sufficiently limited to the detection of IgA against autoantigens in a saliva sample such as oxidized LDL.

Claim Rejections - 35 USC § 112, second paragraph

7. Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is also vague and indefinite because it is a method for diagnosing the likelihood of cardiovascular disease in a patient using a sample from said patient. However, claim 1 recites that the method involves the determination of antibodies against a recombinant antigen or synthetic peptide in said sample. This is confusing since recombinant antigen and synthetic peptide are not generally present in a patient sample. Therefore, it is unclear how antibodies may exist against such antigens.

It is recommended that claim 1, part a) be amended to:

determining a level of antibodies <u>in a saliva sample from said patient</u>, wherein said antibodies are able to bind to an antoantigen or a corresponding recombinant antigen or synthetic peptide for cardiovascular disease; and

Claim 2 is vague and indefinite because it is unclear what kind of immune complexes are being detected or how these unknown immune complexes can be correlated to cardiovascular disease.

Applicant argues that paragraph [0024] of the specification provides support for "immune complexes" as those formed when antigens binds to antibodies and can activate the complement cascade and bind to the C1q component of complement and form pathologic complexes. This argument is not persuasive because, even with this "explanation", it is still unclear what "immune complexes" can be diagnostic for cardiovascular disease. According to the definition of "immune complexes" provided by Applicant, these complexes can be any and all things, therefore, it is confusing since the metes and bounds of the claim cannot be ascertained.

Claim Rejections - 35 USC § 103

8. Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kovanen et al (*Archives of Internal Medicine*. July 13, 1998. Vol. 158, No. 13, pages 1434-1439, IDS) in view of Stone et al., (*Journal of Human Stress*. 1987. Vol. 13, pages 136-140).

Kovanen discloses elevated levels of IgA, IgE and IgG in patients with established arteriosclerosis and myocardial infarction or cardiac death. See page 1435. Kovanen discloses autoantigens and several exogenous antigens as having been implicated in the pathogenesis of myocardial infarction including oxidized LDL and cardiolipin. See page 1437.

Kovanen differs from the instant invention in failing to teach the detection of IgA in saliva.

Stone, however, teaches the measurement of IgA antibody response to a particular antigen in saliva using ELISA. Stone teaches that although IgA is also present in serum, secretory IgA (sIgA) is more advantageous in that it is much larger and binds invading organisms more effectively than serum IgA. Stone also teaches that sIgA can be collected rather simply and inexpensively in saliva and quantitated with a readily available assay. See page 138.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the method of Kovanen to measure sIgA and relating the measured level with diseases such as cardiovascular disease because Stone teaches that sIgA can be measured with ease and the level of sIgA can be directly correlated with immunocompetence. The collection of samples such as saliva is simple and painless and the measurement of sIgA against a specific antigen provides the advantage of a method that has few problems and provides a more meaningful assessment of the sIgA system.

Response to Arguments

9. Applicant's arguments filed 8/30/2004 have been fully considered but they are not persuasive.

Applicant argues that there is no motivation to combine the teachings of Kovanen with Stone because Kovanen fails to recognize the importance of saliva as a source of IgA antibodies against autoantigens and Stone is only concern with sIgA to infectious diseases and not autoantigens. Applicant also argue that there would be no reasonable expectation of success in combining Kovanen and Stone because Stone

discloses that sIgA is different from serum IgA, therefore, one skilled in the art would have no expectation that testing saliva could be used as a reliable test for autoantigens.

These arguments have been fully considered but are not deemed to be persuasive. Kovanen specifically teaches that IgA against oxidized LDL and cardiolipin can be detected and related to the pathogenesis of MI. Kovanen discloses that total levels of antibodies have been determined in patients with atherothrombotic disease and patients with established atherosclerosis have significantly elevated levels of IgA, IgE, IgG and IgM. Stone, on the other hand, discloses that the immunocompetence of an individual can be assessed using the secretory components such as IgA. Stone teaches that sIGA can be collected simply and inexpensively in saliva and quantitated with a readily available assay. Although, it is true that Stone discloses that serum IgA and sIgA are different from each other, specifically sIgA is much larger than serum IgA, this difference is not seen to be an inhibiting factor in detecting sIgA against autoantigens. In fact, one of ordinary skill in the art would have been motivated to use saliva as a sample not only because of the ease with which it can be collected, but also because the larger sIgA would have been more easily detected.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao-Thuy L. Nguyen whose telephone number is (571) 272-0824. The examiner can normally be reached on Tuesday and Thursday from 8:00 a.m. -3:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bao-Thuy L. Nguyen
Primary Examiner
Art Unit 1641
10/15/04